

We claim:

1. A method of identifying a MDP-binding
homing molecule that selectively homes to lung
5 endothelium, comprising:

(a) contacting membrane dipeptidase (MDP)
with one or more molecules; and

(b) determining specific binding of a
molecule to said MDP,

10 wherein the presence of specific binding
identifies said molecule as a MDP-binding homing
molecule that selectively homes to lung endothelium.

2. The method of claim 1, wherein said
MDP is substantially purified.

15 3. The method of claim 2, wherein said
substantially purified MDP is immobilized to a
support.

4. The method of claim 1, wherein said
MDP is human MDP having SEQ ID NO: 448.

20 5. A method of selectively directing a
moiety to lung endothelium in a subject, comprising
administering to said subject a conjugate comprising
a moiety linked to a MDP-binding homing molecule
identified by the method of claim 1,

25 whereby said moiety is selectively directed
to lung endothelium in said subject.

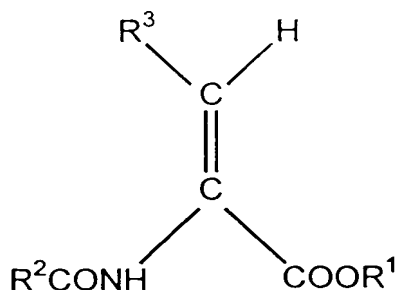
6. The method of claim 5, wherein said MDP-binding homing molecule is a peptide comprising the sequence:



5 wherein X_1 and X_2 each is 1 to 10 independently selected amino acids.

7. The method of claim 6, wherein said MDP-binding homing peptide comprises a sequence selected from the group consisting of CGFECVRQCPERC
10 (SEQ ID NO: 1) and CGFELETC (SEQ ID NO: 2).

8. The method of claim 5, wherein said MDP-binding homing molecule comprises the following Structure 1:



15 wherein R^2 and R^3 are hydrocarbon radicals in the range respectively of 3-10 and 1-15 carbon atoms; in either one of these R^2 or R^3 hydrocarbon chains 1-6 hydrogens may be replaced by halogens or a nonterminal
20 methylene may be replaced by oxygen or sulfur, including oxidized forms of the latter; additionally, a terminal hydrogen in R^3 can also be replaced by hydroxyl or thiol, which

may be acylated or carbamoylated; or the hydrogen can be replaced by amino, which may be derivatized as in an acylamino, ureido, amidino, guanidino, or alkyl or substituted amino group, including quaternary nitrogen grouping; or, there may be replacement by acid groups such as carboxylic, phosphonic or sulfonic acid groups or esters or amides thereof, or cyano; or combinations thereof, such as a terminal amino acid grouping; and R¹ is hydrogen or lower alkyl (C₁₋₆) or dialkylaminoalkyl, or a pharmaceutically acceptable cation.

9. The method of claim 8, wherein said MDP-binding homing molecule is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropane carboxamido)-2-heptenoic acid.

10. The method of claim 8, wherein R² is branched alkyl or cycloalkyl with a limitation that the carbon adjacent to the carbonyl cannot be tertiary.

11. The method of claim 10, wherein R³ is n-alkyl (1-9 carbons) or n-alkyl (1-9 carbons) having a terminal substituent which is a quaternary nitrogen, amine derivative or amino acid derived group.

12. The method of claim 11, wherein R² is 2,2-dimethylcyclopropyl or 2,2-dichlorocyclopropyl and R³ is a hydrocarbon chain of 3 to 7 carbon atoms without a terminal substituent or having a

terminal substituent which is
trimethylammonium, amidino, guanidino or
2-amino-2-carboethylthio.

13. The method of claim 12, wherein
5 said MDP-binding homing molecule is selected
from the group consisting of:

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-
trimethylammonium hydroxide-2-octenoic acid
inner salt;

- 10 Z-2-(2,2-dichlorocyclopropanecarboxamido)-8-
trimethylammonium hydroxide-2-octenoic acid
inner salt;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-
guanidino-2-octenoic acid;

- 15 Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-
guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-
ureido-2-octenoic acid;

- 20 Z-8-(1-2-amino-2-carboxyethylthio)-2-(2,2-
dimethylcyclopropanecarboxamido)-2-octenoic
acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-2-
octenoic acid (racemic and dextrorotatory
forms);

- 25 Z-2-(2,2-dichlorocyclopropanecarboxamido)-2-
octenoic acid;

7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-heptenoic acid; and

6-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-hexenoic acid.

14. The method of claim 5, wherein said moiety is a gene therapy vector.

10 15. The method of claim 5, wherein said moiety is a drug.

16. A method of reducing or preventing lung metastasis in a subject having cancer, comprising administering to said subject a membrane
15 dipeptidase (MDP)-binding homing molecule.

17. The method of claim 16, wherein said MDP-binding homing molecule is a lung homing peptide comprising the sequence:

X_1 -G-F-E- X_2 (SEQ ID NO: 17)

20 wherein X_1 and X_2 each is 1 to 10 independently selected amino acids.

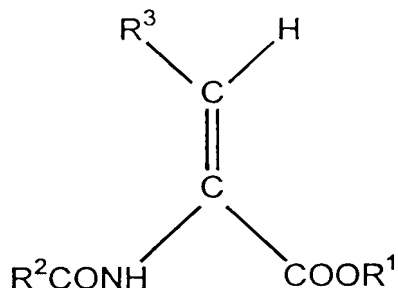
18. The method of claim 17, wherein said MDP-binding homing peptide comprises a sequence selected from the group consisting of CGFECVRQCPCRC
25 (SEQ ID NO: 1) and CGFELETC (SEQ ID NO: 2).

19. The method of claim 18, wherein said MDP-binding homing peptide is a peptide selected from the group consisting of CGFECVRQCPCRC (SEQ ID NO: 1)

and CGFELETC (SEQ ID NO: 2).

20. The method of claim 16, wherein said MDP-binding homing molecule comprises the following Structure 1:

5



wherein R^2 and R^3 are hydrocarbon radicals in the range respectively of 3-10 and 1-15 carbon atoms; in either one of these R^2 or R^3 hydrocarbon chains 1-6 hydrogens may be replaced by halogens or a nonterminal methylene may be replaced by oxygen or sulfur, including oxidized forms of the latter; additionally, a terminal hydrogen in R^3 can also be replaced by hydroxyl or thiol, which may be acylated or carbamoylated; or the hydrogen can be replaced by amino, which may be derivatized as in an acylamino, ureido, amidino, guanidino, or alkyl or substituted amino group, including quaternary nitrogen grouping; or, there may be replacement by acid groups such as carboxylic, phosphonic or sulfonic acid groups or esters or amides thereof, or cyano; or combinations thereof, such as a terminal amino acid grouping; and R^1 is hydrogen or lower alkyl (C_{1-6}) or dialkylaminoalkyl, or a pharmaceutically

acceptable cation.

21. The method of claim 20, wherein
said MDP-binding homing molecule is 7-(L-2-
amino-2-carboxyethylthio)-2-(2,2-
5 dimethylcyclopropane carboxamido)-2-heptenoic
acid.

22. The method of claim 20, wherein
R² is branched alkyl or cycloalkyl with a
limitation that the carbon adjacent to the
10 carbonyl cannot be tertiary.

23. The method of claim 22, wherein
R³ is n-alkyl (1-9 carbons) or n-alkyl (1-9
carbons) having a terminal substituent which
is a quaternary nitrogen, amine derivative or
15 amino acid derived group.

24. The method of claim 23, wherein
R² is 2,2-dimethylcyclopropyl or
2,2-dichlorocyclopropyl and R³ is a
hydrocarbon chain of 3 to 7 carbon atoms
20 without a terminal substituent or having a
terminal substituent which is
trimethylammonium, amidino, guanidino or
2-amino-2-carboxethylthio.

25. The method of claim 24, wherein
25 said MDP-binding homing molecule is selected
from the group consisting of:

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-
trimethylammonium hydroxide-2-octenoic acid
inner salt;

Z-2-(2,2-dichlorocyclopropanecarboxamido)-8-trimethylammonium hydroxide-2-octenoic acid inner salt;

5 Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-ureido-2-octenoic acid;

10 Z-8-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid;

15 Z-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid (racemic and dextrorotatory forms);

Z-2-(2,2-dichlorocyclopropanecarboxamido)-2-octenoic acid;

20 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-heptenoic acid; and

6-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-hexenoic acid.

25 26. The method of claim 16, wherein said MDP-binding homing molecule is an MDP inhibitor.

27. The method of claim 26, wherein said MDP inhibitor exhibits a K_i against MDP of at most 1000 nM.

28. The method of claim 27, wherein said
5 MDP inhibitor exhibits a K_i against MDP of at most 100 nM.

29. The method of claim 28, wherein said MDP inhibitor exhibits a K_i against MDP of at most 1 nM.

10 30. The method of claim 16, wherein said cancer is melanoma.

31. A method of reducing or preventing lung metastasis in a subject having cancer,
15 comprising administering to said subject a membrane dipeptidase (MDP) negative regulatory factor.

32. The method of claim 31, wherein said MDP negative regulatory factor is a soluble MDP polypeptide.

20 33. The method of claim 31, wherein said MDP negative regulatory factor is an antibody that selectively reacts with MDP.

34. A method of reducing or preventing cell homing to lung endothelium in a subject,
25 comprising administering to said subject a membrane dipeptidase (MDP) negative regulatory factor.

35. The method of claim 34, wherein said MDP negative regulatory factor is a soluble MDP polypeptide.

36. The method of claim 34, wherein said MDP negative regulatory factor is an antibody that selectively reacts with MDP.

37. A method of identifying a molecule
5 that reduces or prevents lung metastasis, comprising the steps of:

(a) contacting membrane dipeptidase (MDP) with one or more molecules; and

(b) determining MDP activity in the
10 presence of said molecule as compared to a control value,

wherein diminished MDP activity in the presence of said molecule identifies said molecule as a molecule that reduces or prevents lung metastasis.

38. The method of claim 37, wherein said
15 MDP is substantially purified.

39. The method of claim 37, wherein MDP activity is determined by release of D-Phe from Gly-D-Phe.

40. The method of claim 37, further
20 comprising the steps of:

(c) administering said molecule to a subject having cancer; and

(d) assaying lung metastasis in said
25 subject as compared to a control level of metastasis.